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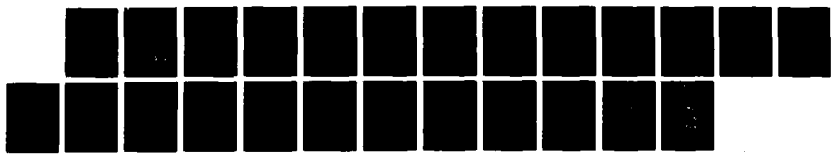

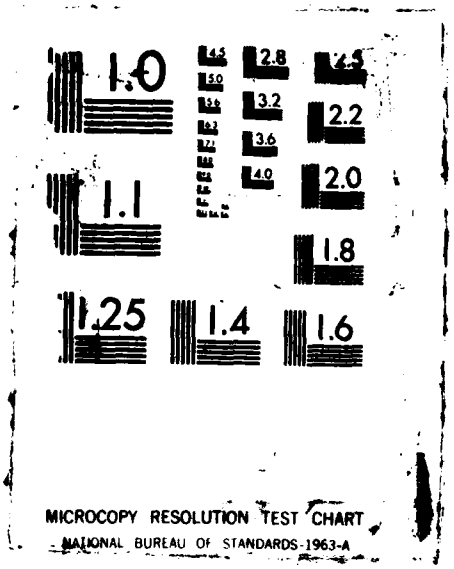
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Atropine-induced cutaneous vasodilation decreases body temperature during exercise

Margaret A. Kolka, Lou A. Stephenson, Anne E. Allan and Paul B. Rock

U.S. Army Research Institute of Environmental Medicine
Natick, MA 01760-5007

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Please address correspondence to:
Margaret A. Kolka
USARIEM
Kansas Street
Natick, MA 01760-5007
(617) 651-4849

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Systemic atropine enhances forearm cutaneous blood flow (FBF) but depresses forearm sweating ($\dot{m}_g$) in warm environments, as previously shown in our laboratory. To further examine thermoregulatory consequences of this increased FBF, four healthy males were studied during 30 minutes of seated exercise (55% $\dot{V}O_2$ peak) in T_a = 22°C, T_{dp} = 4°C. Esophageal (T_{es}) and mean skin ($\bar{T}_{sk}$) temperatures, $\dot{m}_g$, metabolism (M), heart rate (HR) and FBF were measured during control and following 2 mg (im) atropine. Tests were counterbalanced and separated by at least 72 hours. The slope of FBF to T_{es} averaged 1.3 ml·100 ml^{-1}·min^{-1} in control and increased to 8.8 ml·100 ml^{-1}·min^{-1} with atropine ($p<0.05$). All eight skin temperatures increased with atropine ($\bar{T}_{sk}$ = 32.6°C compared to 31.0°C in control), which implies widespread cutaneous vasodilation. The enhanced sensible heat loss with atropine during constant intensity exercise caused T_{es} to decrease, resulting in a further significant $\dot{m}_g$ depression. The decreased central drive did not result in peripheral vasoconstriction, suggesting that the dilation was peripherally controlled and non-responsive to the thermoregulatory controller.

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Key words: cholinergic blockade, skin blood flow, sweating, temperature regulation, vasodilation

Increased cutaneous vasodilation during exercise after systemic atropine administration results in increased sensible (dry) heat loss (when $\bar{T}_{sk} > T_a$) or decreased sensible heat gain (when $\bar{T}_{sk} < T_a$)(4,10,11). This response appears to be mediated peripherally (6), as the sensitivity of increased cutaneous vasodilation to increased core temperature is greater by some 80% during moderate exercise after systemic atropine treatment (14). Some possible mechanisms for the atropine-induced vasodilation may be via 1) a prostaglandin-mediated mechanism (17,25) which functions independently of acetylcholine-mediated vasodilation; 2) a ganglionic release of vasoconstrictor activity (26,27); or 3) the presence of vasodilatory substances associated with the sweat gland (15). However, there may also be a central neural link since atropine has been shown to induce acetylcholine release and turnover in the brain (25). Atropine may induce a cutaneous vasodilation effector signal from the central nervous system.

Although our most recent study of atropine-induced vasodilation in exercising human subjects (14) indicated that there was a peripherally-mediated effect of atropine on the cutaneous vasculature, the experimental design of that study was such that we could not ascertain whether atropine also altered the effector signal from the central nervous system. The current study investigates how the thermoregulatory effectors respond to a changing core temperature after atropine treatment. This study further attempts to characterize the atropine-induced vasodilation during exercise in a cool (22°C) environment using the expected decreased body temperature following the increased sensible heat loss (i.e. vasodilation) as a stimulus for centrally mediated vasoconstriction.

METHODS

Four healthy adult males volunteered following consent procedures by our local Human Use Committee. The average (±SD) age was 20±3 yr, height 181.6 ± 6 cm, weight 71.6 ± 7.5 kg, surface area 1.92 ± 0.06 m^2, body fat 13.4 ± 3.0% and $\dot{V}O_2$ peak 3.67 ± 0.26 $\ell \cdot min^{-1}$.

All testing was performed during February and March when the subjects were not heat acclimated. Subjects were familiarized with all procedures for two weeks before actual experiments began. We tested each subject on at least two occasions in an ambient environmental temperature (T_a) of 22.4°C with an ambient water vapor pressure equal to 0.8 kPa. One test followed the intramuscular (vastus lateralis) injection of 0.281 ±0.003 $mg \cdot kg^{-1}$ atropine sulfate (Elkin-Sinn, Cherry Hill, N.J.) and the other test was after the injection of an equal volume of sterile saline (≈1 ml). Test days on any one subject were separated by a minimum of 72 h, and the experimental order was counterbalanced. All experiments were between 0700 and 1000h, with any individual subject tested at the same hour each day to control for circadian variability in heat loss responses (23). Subjects had not eaten for 12 hours before testing, and were normally hydrated (± 1% of normal body weight).

The experiment lasted one hour, after preliminary thermal equilibration. This included 30 min of rest and 30 min of exercise at 55% of each subject's $\dot{V}O_2$ peak as determined in the week before the first experiment (12,19). Upon arriving at the laboratory, the subject swallowed a catheter containing a thermocouple into his esophagus and adjusted it to heart level to measure core temperature (T_{es}). We required each subject to drink 200 ml of water at this time. Surface thermocouples were placed at eight skin sites to estimate mean skin temperature

($\bar{T}_{sk}$) as:

$\bar{T}_{sk}$ = 0.07(head) + 0.175(chest) + 0.175(back) + 0.07(upper arm) + 0.07(forearm) + 0.05(hand) + 0.19(thigh) + 0.20(calf) (20).

An automatic dew-point sensor enclosed in a ventilated capsule was attached to the volar surface of the forearm to measure local sweating rate as described earlier (12). These sensors were ventilated with ambient air from the chamber at a flow rate of 600 ml•min^{-1}. A mercury-in-silastic strain gauge was placed on the contralateral forearm for the measurement of forearm blood flow (FBF) by venous occlusion plethysmography (7,28). Temperatures and sweating were recorded continuously and FBF was measured twice each minute. Heart rate (HR) was recorded frequently and metabolic heat production (M) was estimated at rest and from 20 to 25 minutes of exercise by open circuit spirometry.

The T_{es} thresholds for cutaneous vasodilation and arm sweating were calculated for each experiment by analyzing the transient phase of the FBF to T_{es} and $\dot{m}_s$ to T_{es} relationships during exercise. An individual regression was calculated for each subject for each experiment. The T_{es} threshold for sweating (defined as T_{es} intercept) was calculated from the regression equation at $\dot{m}_s$= 0.06 mg•cm^{-2}•min^{-1} (1), whereas the T_{es} threshold for vasodilation was calculated from the regression equation at the average resting blood flow measured for each subject in a thermally comfortable environment.

All data were analyzed by ANOVA with repeated measures. Tukey's test of critical difference was used when appropriate. All differences in the results are significant at $p<0.05$ unless otherwise noted.

RESULTS

The time course for T_{es} and $\bar{T}_{sk}$ is presented in Figure 1 and Figure 2 for one representative subject during both atropine and saline experiments. Note that T_{es} increased at the beginning of exercise but levelled off after approximately 15 minutes in the saline experiment. During the atropine experiments, T_{es} actually decreased after the initial increase during constant exercise. $\bar{T}_{sk}$ was relatively constant in saline experiments and increased during exercise after atropine. The reason for the responses seen in T_{es} and $\bar{T}_{sk}$ becomes clear as we look at Figure 3 (data from the same subject). Cutaneous blood flow during exercise after atropine was clearly enhanced and resulted in a greatly increased dry heat loss manifested in the reduced T_{es} shown in Figure 1 beginning at approximately minute 12. Although arm sweating was already inhibited significantly with atropine treatment (-0.33 $mg \cdot cm^{-2} \cdot min^{-1}$, -54%) by minute twelve, this decreased T_{es} was associated with a further decrease in sweating (-0.17 $mg \cdot cm^{-2} \cdot min^{-1}$) as shown for the same subject in Figure 4. The increased skin blood flow visually appears to be widespread as apparent by increases in local T_{sk} of all skin sites measured except the hand (same subject, Figure 5) during the measured vasodilation. The hand temperature increase was delayed approximately 5 minutes compared to other skin sites.

The $\dot{m}_s$ to T_{es} and FBF to T_{es} slopes and intercepts are given in Table 1 and Table 2 for the four subjects during both control and atropine experiments. Note the increase in the slope of FBF to T_{es} ($p<0.01$) in atropine experiments and decrease in the slope of $\dot{m}_s$ to T_{es} ($p=0.11$). The T_{es} threshold for $\dot{m}_s$ was elevated 0.3°C ($p<0.01$) and rightward shifted for FBF (0.3°C, $p=0.17$). The sweating onset time during exercise was delayed an average of six minutes by atropine ($p=0.10$). Onset time for vasodilation determined by FBF, however,

occurred nine minutes earlier ($p=0.01$) in atropine experiments. Whole body sweating averaged 9.4 ± 3.3 $g \cdot min^{-1}$ in control experiments, and 4.0 ± 2.7 $g \cdot min^{-1}$ in atropine experiments, an average decrease of 57% ($p<0.05$). The mean thermoregulatory parameters measured during rest and at 25 minutes of exercise are given in Table 3. These data represent steady-state values and are not representative of the transient responses reported above.

DISCUSSION

The sensitivity of cutaneous vasodilatory responses to increasing core (T_{es}) temperature is enhanced during exercise and recovery from exercise after atropine administration (13,14). This vasodilation can contribute to increased heat loss when $\bar{T}_{sk} > T_a$ (11,13) or reduced heat gain in environments where $\bar{T}_{sk} < T_a$ (4,10,11) compared to saline treated individuals. In general, the responses seen at 22° C in the present study are similar to those found during exposure to a warmer temperature (14). The onset time of FBF was earlier, the sensitivity greater and there occurred a tendancy for the esophageal threshold for vasodilation to be at a lower core temperature after atropine treatment. Local sweating responses indicated a delayed onset time, an elevated esophageal temperature threshold and a tendancy for reduced sensitivity.

The present study provides initial evidence that cutaneous vasodilation can occur during exercise in a cool environment after systemic atropine administration in excess of that seen at the same core temperature in control experiments. This enhanced cutaneous vasodilation during moderate exercise was accompanied by a reduction in core temperature during constant intensity exercise (Figure 1). Interestingly, as core temperature decreased during exercise as a result of the augmented dry heat loss in atropine experiments, the local sweating response was

depressed further (Figure 4). The decreased core temperature resulted in decreased efferent activity to the sweat glands, further reducing evaporative heat loss (3). Figure 6 shows that a rising curve of arm sweating accompanying the increasing core temperature is followed by a decreasing arm sweating as core temperature decreases with the vasodilation after atropine. However, there was no concomitant cutaneous vasoconstriction associated with this further suppression in sweating during the constant intensity exercise as core temperature decreased (Figure 3). This dissociation between these effector responses suggests that the atropine-induced vasodilation is a peripherally controlled response that is not under the direct control of the CNS thermoregulatory controller. In our earlier studies of cutaneous vasodilation during exercise after atropine administration (10,11,13), we suggested that a peripheral mode of action was the more dominant effect, a finding substantiated by the current study.

The local skin temperature at the forearm, (as well as the mean weighted skin temperature) was in the range where vasoconstriction is the primary cutaneous vascular response (8,18,27), a point substantiated by the low slopes seen for FBF to T_{es}. In spite of this cool skin temperature ($\approx 30^{\circ}C$), vasodilation occurred following atropine injection during exercise in excess of that seen in the control experiments. Following the enhanced vasodilation, the decreased core temperature did not result in increased vasoconstrictor activity of the cutaneous vascular beds even as sweating was decreased. It appears that the central thermal control signal to reduce forearm cutaneous blood flow was absent or overridden by local factors in the atropine treated subjects. Furthermore, the control of FBF does not have to be totally coupled with sweat secretion.

The mechanism for the vasodilatory response during exercise after atropine treatment in the presence of a cool skin and decreasing core temperature is still not clear. A release of vasoconstriction at the ganglionic level probably would not result in blood flow differences as large as seen in the present study (27). As we previously suggested (14) these observations are consistent with the presence of vasodilatory substances associated with the sweat gland (24) of which one may be vasoactive intestinal polypeptide (VIP)(16,21) or some other vasodilatory substance that may act through a non-acetylcholine-like mechanism (2). Lundberg (16) has presented evidence that VIP may be responsible for the atropine-resistant vasodilation in sweat glands of the cat and other exocrine organs, since secretion from sweat glands is accompanied by a marked non-cholinergic increase in blood flow (5,16). It has been proposed (16) that sweat secretion involves a 1) stimulation of the secretory cells, 2) stimulation of myoepithelial cells, 3) direct stimulation of vasodilatory nerves, and 4) indirect stimulation of blood flow via vasodilatory substances. Rowell (22) in a recent review presented evidence against an earlier hypothesis linking bradykinin to this vasodilation (15).

If a vasodilatory substance were coupled with sweat gland stimulation, then as body temperature decreased during exercise in atropine experiments and caused a further decreased sweat gland secretion (and probably stimulation), a reversal of the cutaneous vasodilation would follow. However, this was not the case in any of the four subjects, all of whom showed the general suppression in sweat gland secretion after T_{es} decreased in the atropine experiments. Even though the cutaneous vasodilation persisted after further sweating depression occurred, we cannot completely rule out the existence of a vasodilatory substance which is linked to sweating. It may be that such a vasodilatory substance if it exists could be

metabolized slowly and remained active in the skin even though sweat gland stimulation was attenuated (Fig. 4). The half-life of VIP in tissue homogenates is 1 to 1.5 minutes (9) which would appear to limit the involvement of this peptide in the atropine vasodilation. However, the VIP-receptor dissociation constant as determined from uterine smooth muscle was biexponential (70% slow state) and indicates a much slower turnover of this peptide once it is bound to a receptor (21).

The presence of a non-cholinergic mechanism still appears to be a plausible mechanism for atropine-induced cutaneous vasodilation, which cannot be substantiated or refuted by the present data. A more specifically designed experiment will be necessary to examine this possibility. This study also provides evidence that atropine itself did not block the response of the thermoregulatory controller to changing core temperature. The observation of a further suppression of the sweating rate after T_{es} decreased during exercise after atropine indicated that the efferent activity was appropriately reduced (Figure 6). We interpret this as a result of reduced efferent activity since the thermoregulatory controller responded appropriately to decreased T_{es}. Yet, at the beginning of exercise, atropine elicited an elevated T_{es} threshold for onset of sweating. Such a response has been classically interpreted (6) as evidence that the thermoregulatory perturbation had occurred via a centrally-mediated mechanism. This interpretation is not entirely appropriate for the present study because the efferent signal for sweating was appropriately reduced when T_{es} decreased during exercise.

The widespread increase in cutaneous blood flow during exercise in a cool environment after atropine treatment decreased body temperature and resulted in further suppression of eccrine sweating, thereby lowering evaporative heat loss.

The lower central thermal drive did not impact on the enhanced cutaneous vasodilation, implying that such dilation was peripherally controlled and non-responsive to the thermoregulatory controller. However, tight central thermoregulatory control of sweating was maintained as apparent by the increased or decreased activation of this response in proportion to core temperature drive.

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Human subjects participated in these studies after giving their free and informed consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on the Use of Volunteers in Research.

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FIGURE LEGENDS

Figure 1. Time course for esophageal temperature for a representative subject during control and atropine experiments. Time = 0, exercise begins, drug injection was at -30.

Figure 2. Mean weighted skin temperature (eight sites) during control and atropine experiments for a single subject. Time = 0 exercise begins, atropine injection at -30.

Figure 3. Forearm cutaneous blood flow for one subject in both control and atropine experiments. Time = 0 exercise begins, atropine injection at -30.

Figure 4. Forearm sweating for a representative subject during control and atropine experiments. Time = 0 exercise begins, atropine injection at -30.

Figure 5. Local skin surface temperatures for one subject after atropine injection at -30 min. Exercise began at Time = 0. The forearm thermocouple was attached at Time = 10, which coincides with the initiation of FBF measurements.

Figure 6. Forearm sweating to esophageal temperature for a single subject during atropine and saline experiments. The open triangles (Δ) represent the depressed sweating after the atropine vasodilation.

Table 1. Slope and T_{es} threshold for local sweating to esophageal temperature and onset time for sweating during exercise.

	$\dot{m}_s$ slope ($mg \cdot min^{-1} \cdot cm^{-2} \cdot {}^oC^{-1}$)	$\dot{m}_s$ threshold (^oC)	$\dot{m}_s$ onset (min)
CONTROL			
1	0.94	36.8	5
2	1.25	36.8	7
3	1.09	37.0	5
4	1.25	37.2	5
MEAN	1.13	36.7	5.5
SD	(0.15)	(0.19)	(1.0)
ATROPINE			
1	0.62	37.1	10
2	1.26	37.1	8
3	0.46	37.3	10
4	0.25	37.5	18
MEAN	0.65	37.3**	11.5**
SD	(0.43)	(0.19)	(4.4)

** $p<0.01$
The numbers 1 through 4 are the subject numbers

Table 2. Slope and T_{es} threshold for cutaneous vasodilation (FBF) to esophageal temperature and onset time for cutaneous vasodilation during exercise.

	FBF slope ($ml \cdot 100ml^{-1} \cdot min^{-1} \cdot {}^{o}C^{-1}$)	FBF threshold (^{o}C)	FBF onset (min)
CONTROL			
1	1.03	37.3	25
2	1.92	37.2	15
3	2.90	37.5	19
4	3.33	37.4	10
MEAN	2.30	37.4	17.3
SD	(1.03)	(0.13)	(6.3)
ATROPINE			
1	7.25	37.2	12
2	8.19	37.1	10
3	10.23	37.3	10
4	9.36	36.6	1
MEAN	8.76**	37.1	8.3**
SD	(1.31)	(0.31)	(4.9)

** $p<0.01$
The numbers 1 through 4 are the subject numbers

Table 3. Individual thermoregulatory data for four subjects at rest and at 25 min of cycle exercise in control and atropine experiments.

	T_{es}	$\bar{T}_{sk}$	$\bar{T}_b$	$\dot{s}_g$	FBF	M	HR
	(°C)	(°C)	(°C)	($mg \cdot cm^{-2} \cdot min^{-1}$)	($ml \cdot 100ml^{-1} \cdot min^{-1}$)	($W \cdot m^{-2}$)	(bpm)
CONTROL							
1	36.60	29.91	35.26	0.07	0.1	42	66
2	36.67	29.79	35.29	0.07	0.3	38	55
3	36.85	30.74	35.63	0.07	0.1	40	59
4	37.05	30.71	35.83	0.05	1.2	51	95
MEAN	36.79	30.29	35.50	0.07	0.4	43	69
SD	(0.20)	(0.51)	(0.28)	(0.01)	(0.06)	(6)	(18)
ATROPINE							
1	36.72	29.73	35.32	0.06	0.1	62	71
2	36.89	30.22	35.56	0.08	0.4	44	87
3	36.65	30.47	35.42	0.07	0.4	50	76
4	36.98	30.12	35.61	0.06	0.5	42	111
MEAN	36.81	30.14	35.48	0.07	0.4	50	86*
SD	(0.15)	(0.31)	(0.13)	(0.01)	(0.2)	(9)	(18)
EXERCISE							
CONTROL							
1	37.33	29.76	35.82	1.06	0.8	310	115
2	37.28	31.28	36.08	0.82	2.7	440	140
3	37.50	32.75	36.55	0.61	8.5	378	147
4	37.32	30.23	35.90	0.57	4.3	287	150
MEAN	37.36	31.01	36.09	0.77	4.1	354	138
SD	(0.10)	(1.33)	(0.33)	(0.23)	(3.3)	(69)	(16)
ATROPINE							
1	37.30	31.73	36.19	0.36	3.5	351	145
2	37.02	33.21	36.26	0.43	7.7	382	163
3	37.54	33.41	36.71	0.13	12.3	376	164
4	37.19	31.89	36.13	0.09	8.8	289	177
MEAN	37.26	32.56**	36.32	0.25**	8.1**	350	162**
SD	(0.22)	(0.87)	(0.26)	(0.17)	(3.6)	(43)	(13)

* $p<0.05$ from control
** $p<0.01$ from control

Fig. 1

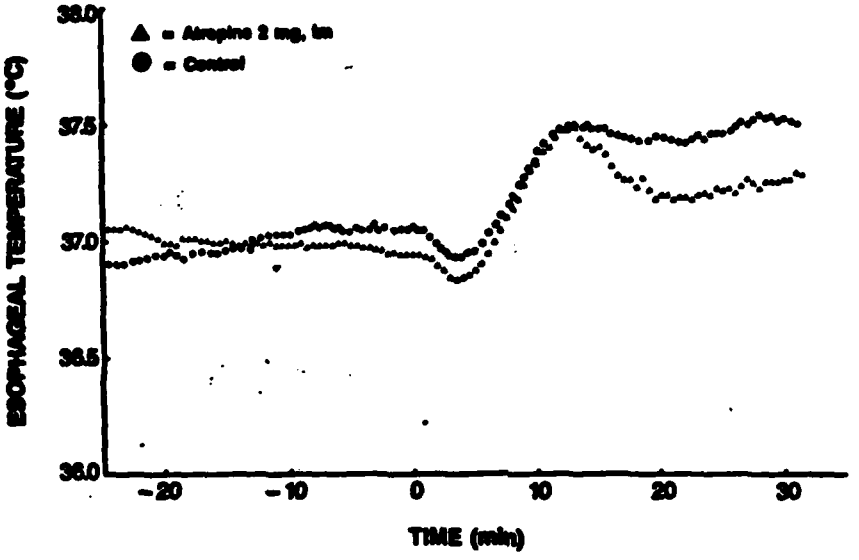


Fig. 2

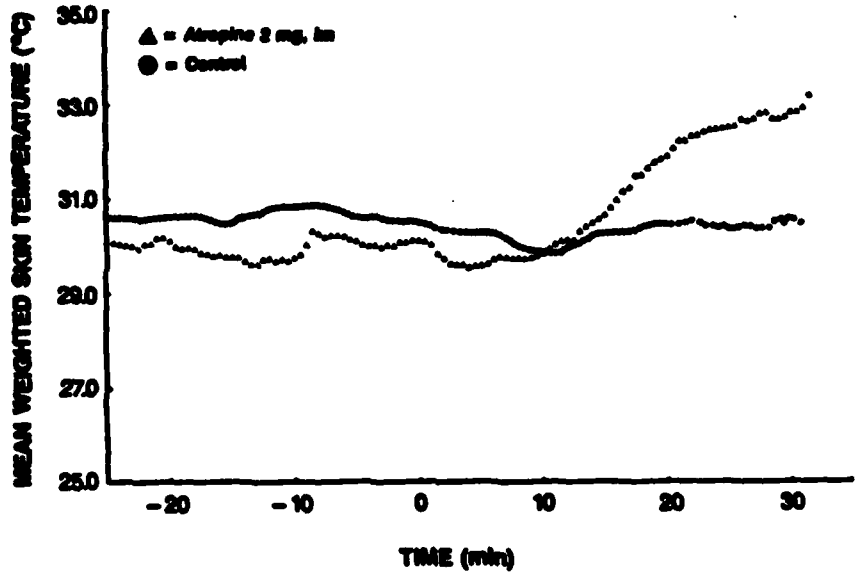


Fig. 3

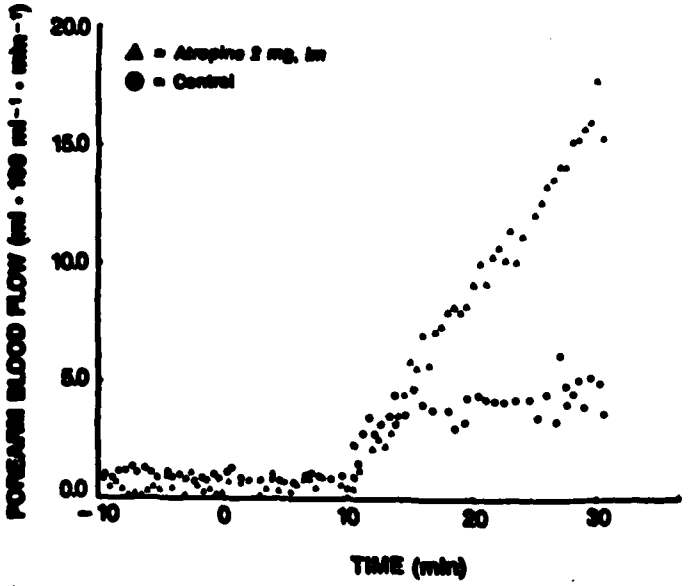


Fig. 4

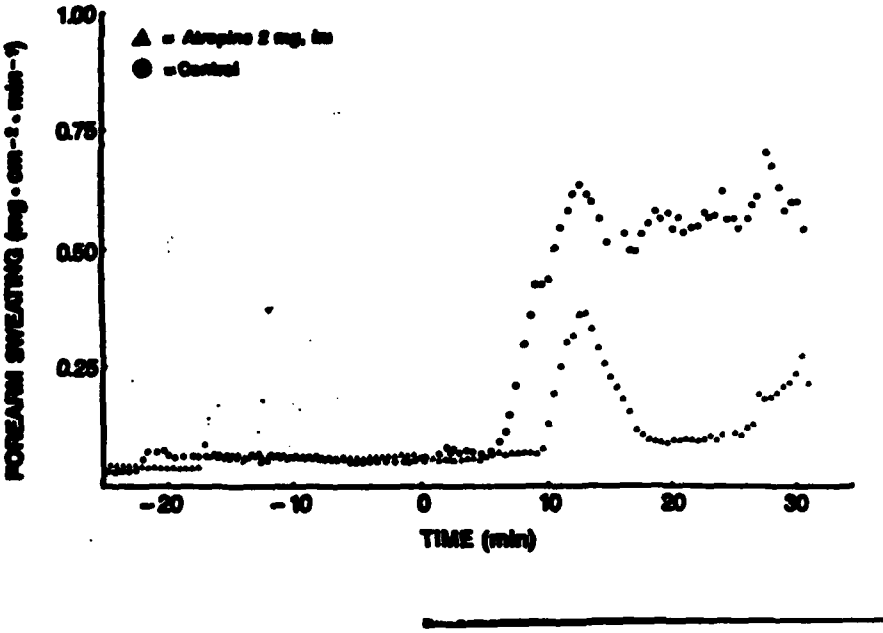


Fig. 5

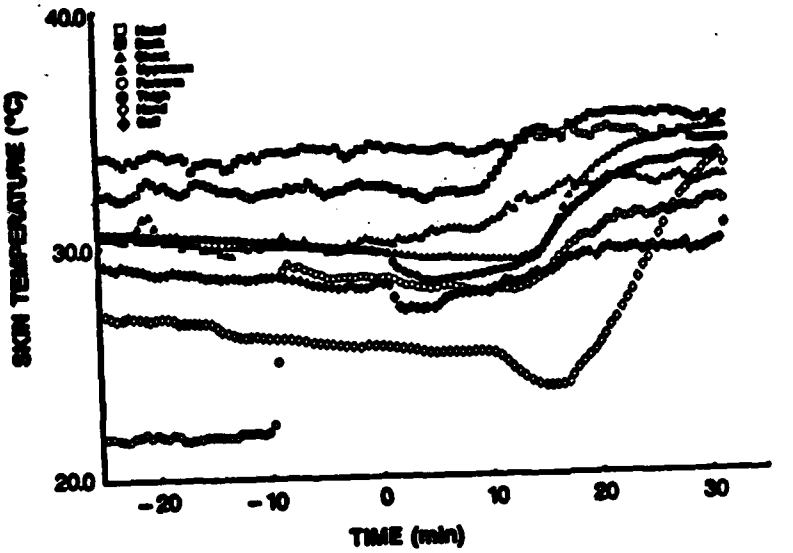
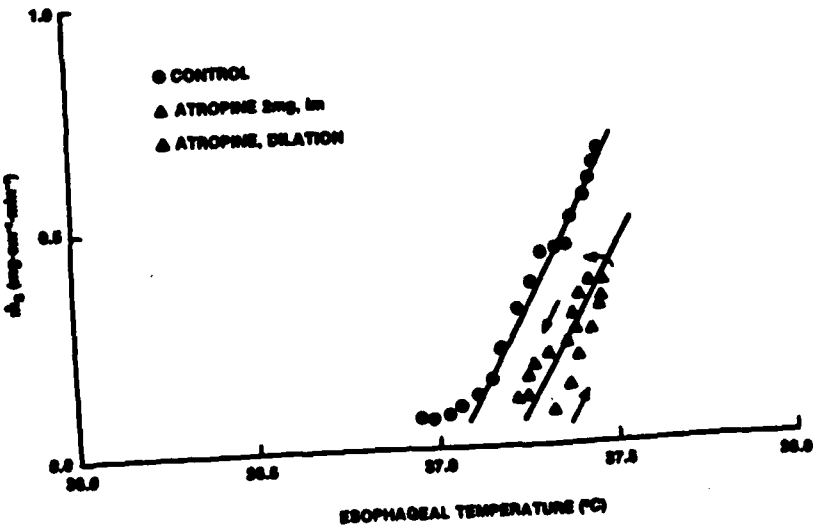


Fig. 6



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